Docket 17006CON1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: AOKI et al.) O. Chernyshev.
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Serial Number: 09/812,113) Art Unit 1646
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Filed: March 15, 2001)
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For: METHODS FOR TREATING NEUROMUSCULAR)
DISORDERS WITH BOTULINUM TOXIN)
TYPES A AND B) Irvine, California

RESPONSE TO OFFICE ACTION

Assistant Commissioner of Patents
Washington, D.C. 20231

REMARKS

I. The Office Action

The December 20, 2001 office action (the "Office Action") in this application:

(1) requested a new oath or declaration;

(2) objected to claims 13 and 17 because of informalities;

(3) rejected claims 1, 4 and 11-19 under 35 U.S.C. section 112, first paragraph, and;

(4) rejected claims 1, 4 and 11-19 under 35 U.S.C. section 112, second paragraph.

Applicants respond to the Office Action as follows.

II. The Declaration

The Office Action requested a new oath or declaration because the declaration submitted "does not identify the post office address of each inventor" (Office Action, page 2).

Enclosed is a copy of the declaration submitted with the present continuation application serial number 09/812,113 when it was filed on March 15, 2001. The declaration submitted identifies the four co-inventors and, immediately under the signature of each inventor, sets forth his or her complete residence address, including the zip code.

For this reason, withdrawal of the request for a new oath or declaration is requested.

III. Objection to Claims 13 and 17

Claims 13 and 17 were objected to because these claims do not end in a period. These claims have been amended to overcome this objection and withdrawal of the objection is therefore requested.

IV. The Section 112(1) Rejection

The Office Action rejected claims 1, 4 and 11-19 under 35 U.S.C. section 112, first paragraph as being nonenabling claims because the claimed "neuromuscular disorders is extremely broad" (page 4 of the Office Action) and the various neuromuscular disorders "have different origin, etiology and

development" (page 4 of the Office Action) and "Therefore, one skilled in the art would not expect that the administration of botulinum toxin type A followed by the administration of botulinum toxin type B would lead to the treatment of all possible 'neuromuscular disorders' and conditions" (page 4 of the Office Action). Pages 5-6 of the Office Action point to alleged deficiencies in the specification such that the specification, it is stated, does not provide adequate support to enable practice of the claimed invention without undue experimentation.

Respectfully, applicants disagree, and wish to make the following points in pursuit of a withdrawal of the rejection:

I. The claims in this application are limited to administration of botulinum toxin type A toxin followed by administration of botulinum toxin type B, where the patient shows a diminished response to the botulinum toxin type A, or alternately to; administration of botulinum toxin type B to a patient who already presents with a diminished response to the type A toxin.

II. It is well known that botulinum toxin has a high and specific affinity for pre-synaptic receptors on neurons at the neuromuscular junction, where the toxin act as an intracellular protease to inhibit release of acetylcholine. Thus, although the botulinum toxins are classified as neurotoxins, their effect on neurons at the neuromuscular junction is local (upon intramuscular or subcutaneous injection of the toxin) and reversible. See e.g. Gracies, J-M., et al, *Botulinum toxin therapy*, Neurologist 2000;6(2):98-115 (attached). These unique properties of botulinum toxin have led to its' widespread clinical use, long before the filing of the present patent application, for the treatment of numerous disorders of muscle innervation (i.e. "neuromuscular disorders"), as will be detailed below.

III. Contrary to what is stated on page 4 of the Office Action, the term "neuromuscular disorders" is still very much is use. For example, a web site search reveals 1700 separate hits for the phrase "neuromuscular disorders" in

conjunction with the word botulinum. See the attached three page web page search results print out, dated March 4, 2002.

Additionally, the medical literature in peer reviewed journals consistently refers to botulinum toxin as being used to treat "neuromuscular disorders" see e.g.., Koman L.A., et al., *Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trail. BOTOX study group*, J Pediatr Orthop 2000 Jan-Feb;20(1):108-115 (abstract enclosed), and; Johnson E.A., *Clostridial toxins as therapeutic agents;Benefits of nature's most toxin proteins*, Annu Rev Microbiol 1999;53:551-75 (abstract enclosed).

IV. Applicants agree that the phrase "neuromuscular disorders", as used in the claims, encompasses a broad number of "disorders that are characterized by the muscle abnormalities caused by dysfunction of muscle enervation" (page 4 of the Office Action). Importantly, botulinum toxin have been used to successfully treat a broad variety of "disorders that are characterized by the muscle abnormalities caused by dysfunction of muscle enervation" (i.e. neuromuscular disorders) (page 4 of the Office Action). Thus, although "neuromuscular disorders" is a broad term it correctly describes the broad therapeutic value of botulinum toxin, since, as stated, botulinum toxin has in fact been used to treat a broad variety of "neuromuscular disorders."

The art clearly shows that botulinum toxins had been used extensively and successfully to treat broad and diverse neuromuscular disorders long before the effective filing date (June 10, 1993) of the present application, and therefore, prior to the 1993 effective filing date of the present patent application it was known by those of ordinary skill in the art to administer botulinum toxin type A to patients to treat a variety of neuromuscular disorders.

For example:

(a) successful clinical use (i.e. injection into humans for a therapeutic effect) of type A toxin was reported at least as early as 1980: Scott A.B., *Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery*, Ophthalmology 1980;87(10):1044-9;

(b) it was reported in 1990 that "Botulinum toxin is a very effective and safe method of treatment for spasmodic torticollis, Lorentz, I.T., et al., *Treatment of idiopathic spasmodic torticollis with botulinum-A toxin: A pilot study of 19 patients,* Med J Aust 1990;152(10):528-30. "Spasmodic torticollis" is a synonym for "cervical dystonia".

(c) it was also reported in 1990 that "botulinum toxin injections are a safe and effective therapy for patients with focal dystonia and hemifacial spasm", Jankovic J., et al., *Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm*, J Neurol Neurosurg Psychiatry 1990;53(8):633-639

(d) it was reported in 1992 that:

1) "botulinum toxin therapy is safe and effective for treating strabismus, blepharospasm, hemifacial spasm, adductor spasmodic dysphonia, jaw-closing oromandibular dystonia, and cervical dystonia", Sataloff R.T., et al., *Botulinum toxin: National institutes of health consensus development panel on clinical use of botulinum toxin*, J Voice 1992;6(4):394-400 (abstract enclosed).

2) "Treatment with botulinum type A toxin has provided welcome relief and hope for patients with adult onset focal dystonias...", Lees A. J., *Botulinum toxin*, Br Med J 1992;305(6863):1169-1170(abstract enclosed).

3) "Botulinum toxin therapy is proving very useful in the treatment of focal dystonias", Markham C.H., *The dystonias*, Curr Opin Neurol Neurosurg 1992;5(3):301-307 (abstract enclosed).

4) "Botox (botulinum toxin type A) is accepted as a safe and efficacious modality for the treatment of cervical dystonia", Metzer W.S., et al., *Treatment of cervical dystonia (torticollis) in adults with botulinum A toxin*, J Ark Med Soc 1992;89(3):133-4 (abstract enclosed).

5) "It is concluded that local botulinum toxin injections can be a safe and efficacious long-term treatment of spasmodic torticollis", Poewe W., et al., *Treatment of spasmodic torticollis with local injections of botulinum toxin: one year follow-up in 37 patients*, J Neurol 1992;239(1):21-25 (abstract enclosed).

The art continues to report numerous uses of botulinum toxin with regard to treatment of neuromuscular disorders. See e.g. (a) the enclosed table of contents from Jankovic, J., et al., *Therapy with botulinum toxin*, Marcel Dekker, Inc. (1994), and; (b) Blitzer A., et al., *Botulinum toxin:basic science and clinical uses in otolaryngology*, Laryngoscope 2001 Feb;111(2):218-26 (abstract enclosed).

Thus, botulinum toxin has been used to treat numerous neuromuscular disorders including dystonias, blepharospasm, cervical dystonia, focal dystonia, spasm, strabismus, spasmodic dysphonia, oromandibular dystonia, laryngeal dystonia, tremors, tics, cerebral palsy, spasticity, dyssynergia, myoclonus, Parkinson's disease, anismus, stuttering, and headache.

(e) Furthermore, botulinum toxin type B was isolated at least as early as 1977 (DasGupta B.R., *Comparative sizes of type A and B botulinum neurotoxins*, Toxicon 1977;15:357-63, abstract enclosed) and prior to the effective filing date of the present patent application it was known to administer botulinum toxin type

F to patients with a diminished clinical response (i.e. due to the presence of antibodies to the type A toxin) to botulinum toxin type A. Ludlow C.L. et al., *Botulinum toxin type F treatment of patients with botulinum toxin type A antibodies*, Mov Disord 1992;7(Suppl 1):133 P400) (abstract enclosed).

Hence, the teaching of the relevant art clearly provided knowledge to one of ordinary skill in the art prior to the effective filing date of the present patent application that botulinum toxin type A can be used to treat numerous neuromuscular disorders. Additionally, the art also shows that botulinum toxin type F had been used in those patient who have antibodies to the type A toxin. Hence, the art provides abundant relevant guidance (for the purpose of enablement) with regard to the practice of the claimed invention: that botulinum toxin type B can be used with therapeutic effect in those patients who have shown a diminished clinical response to administration of botulinum toxin type A.

Thus, the evidence sets forth above clearly shows that: (1) botulinum toxin is properly characterized as treating the afflictions encompassed by the broad term "neuromuscular disorders", (2) that the term "neuromuscular disorders" is in current use in the art, and (3) that there was a high level of skill in the art with regard to the claimed invention, since doctors had *at least 13 years of experience in the therapeutic use of botulinum toxin type A* to treat various neuromuscular disorders prior to the effective filing date of the present patent application. Additionally, in 1989 the FDA approved botulinum toxin type A for use in the treatment of strabismus, blepharospasm and hemifacial spasm.

Respectfully, the Office Action has presented no evidence to the contrary with regard to any of the points (1) to (3) in the paragraph above. The excerpts provided by the Office Action of certain pages from the Merck Manual merely show that publications' preference to classify certain diseases as "disorders of neuromuscular transmission" or as "muscular dystrophies" The excerpts provided from the Merck manual do not anywhere state or indicate that

botulinum toxin does not have therapeutic use to broadly treat neuromuscular disorders or that "neuromuscular disorders" is not a term of art in use by doctors.

V. Page 5 of the Office Action states that insufficient guidance is provided in the application to teach how to carry out the present invention. Respectively, the Office Action is mistaken. Thus, page 5 of the Office Action states that "route of administration" is not specified. But, it is well known that botulinum toxin is always administered by an intramuscular or subcutaneous injection at the site of the afflicted muscles – otherwise botulism would result (i.e. upon entry of the toxin into the circulatory system). Additionally, page 9, line 33 of the specification, continuing to page 10, line 8 of the specification states that administration is by intramuscular or subcutaneous routes.

Additionally, the guidance provided by the specification includes teachings of the claimed method: see e.g. Example 1 on page 13 of the specification which disclose a method within the scope of the present claims. Additionally, page 9, line 32, continuing to page 11 line 33 provide further guidance regarding route of administration, formulations, and dosages.

Furthermore, as set forth above, it was well within the skill of the person of ordinary skill (i.e. a medical doctor with training in the treatment of neuromuscular disorders) as of the 1993 effective filing date of this application to administer botulinum toxin type B to a patient who has experienced a loss of clinical effectiveness to the administered type A toxin, since doctors have been administering type A toxin to patients since about 1980 and the availability of type B toxin was known since about 1977 (see above).

Hence, applicants' specification need not and is not required to set out the details of clinical practice of the claimed method since the attending physician is already experienced in the use of botulinum toxin and must use his or her discretion with regard to patient specific factors such as the particular dose

amount, route of administration, time of administration, etc. Note that, as presaged by applicants' invention, clinical use of type B toxin in type A resistant patients is now known: Brin, M.F., et al., *Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia*, Neurology 53; 1431-1438 (1999) (copy attached).

The Office Action states on page 6 that the lack of teaching and unpredictability of the art" argues for non-enablement of the claimed invention. Surely, the abundant pre-1993 literature with regard to clinical use of botulinum toxin (as set forth above), and the formal approvals by the FDA (in 1989 and 2000) for the use of botulinum toxins types A and B to treat various neuromuscular disorders, refutes this assertion and point instead to prolific teachings in the art relevant to the claimed invention and to a high level of predictability of the art - there is clinical experience of successful use of botulinum toxin going back more than a decade prior to the filing date of this application.

For these reasons, withdraw of the section 112, first paragraph rejection is requested.

V. Rejection Under 35 U.S.C. Section 112, Second Paragraph

The Office Action rejected claims 1,4 and 11-19 under 35 U.S.C. section 112, second paragraph on the bases that four different phrases used in the rejected claims are not clear:

1. The Phrase "Therapeutically Effective Amount"

Claims 1, 4,12 and 16 were rejected under section 112(2) for use of the phrase "therapeutically effective amount."

Please note that the assignee of the present application has obtained at least the following fourteen U.S. patents all of which claim use of a "therapeutically effective amount" of a botulinum toxin: 6,350,455; 6,337,075; 6,333,037; 6,328,977; 6,319,506; 6,319,505; 6,306,403; 6,290,961; 6,265,379; 6,261,572; 6,236,289; 6,143,306; 6,139,845 and; 6,113,915. Additionally, it is well known that the claims are read in conjunction with the specification, and the present application at page 10, line 33, continuing to page 11, line 33 provides guidance as to what a "therapeutically effective amount" is within the scope of the present claims. Furthermore, the prior art (as cited in the section above) provides abundant evidence as to the use of therapeutically effective amounts of different botulinum toxins in humans to treat a variety of neuromuscular disorders. Hence, it is submitted that the person of ordinary skill in the art understands that a "therapeutically effective amount" is that amount which will achieve the desired therapeutic effect and with his or her knowledge of the art can easily select the amount of toxin required for this purpose.

2. The Phrase "Diminished Clinical Effectiveness"

Claim 12 was rejected under section 112(2) for use of the phrase "diminished clinical effectiveness"

Respectfully, it is known and understood in the art that the phrase "diminished clinical effectiveness" in claim 12 means that administration of type A toxin no longer provides the same clinical effectiveness. Nevertheless without conceding that this phrase is unclear, but to expedite prosecution, applicants have amended claim 12 to remove this basis for this section 112, second paragraph rejection.

3. The Phrase "Abnormal Head Position Symptom"

Claim 14 was rejected under section 112(1) for use of the phrase "abnormal head position symptom."

Claim 14 is limited to treatment of cervical dystonia. As shown by the attached publication located at www.herbs4st.com/spasmodictorticollis.htm, it is well known that an "abnormal head position" is symptomatic of cervical dystonia. Therefore the phrase "abnormal head position" is well understood by those of ordinary skill in the field of the claimed invention. Hence, the claimed treatment of an abnormal head position symptom does not introduce any lack of clarity into claim 14.

4. The Phrases "Reduces the Severity" and "Reduces the Neck Pain"

The Office Action rejected claims 14, 15, 18 and 19 under 35 U.S.C. section 112, second paragraph for use of the phrases "reduces the severity" and "reduces the neck pain" in those claims. The Office Action states (page 7) "It is not apparent from the claims how much is the reduction of the severity of the symptoms is intended." Thus, the Office Action has rejected the quoted two phrases in the claims due to use of the word "reduces" in these phrases.

Applicant's invention, as set forth in the rejected claims 14, 15, 18 and 19, encompasses use of the claimed method to treat cervical dystonia. In other words, applicants invention encompasses: (1) a complete elimination, (2) a slight reduction, (3) a significant reduction and (4) a near entire removal of an abnormal head position symptom (claims 14 and 18) or of a neck pain associated with cervical dystonia (claims 18 and 19), all of these being desirable therapeutic outcomes which are included within the scope of the word "reduces." Respectfully, the person of ordinary skill in the filed of the claimed invention (i.e. a doctor with training in the treatment of movement disorders) clearly understands that any reduction (total or partial) of either an abnormal head

position symptom or a neck pain associated with cervical dystonia is a desirable outcome.

Hence the word "reduces" does not introduce any lack of clarity into either of the rejected phrases, and to require applicant to amend or remove this word from the rejected claims would serve only to prevent applicants from claiming the full scope of their invention to which they are entitled.

VI. Conclusion

All issues raised by the Office Action have been addressed. Examination and allowance of claims 1, 4 and 11-19 is requested.

Respectfully Submitted,

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I hereby certify that Response to Office Action and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date March 7, 2002 in an envelope as "Express Mail Post Office to Addressee" Mailing Label number **EL897833695US** addressed to Assistant Commissioner for Patents, Washington, D.C. 20231

Susan Bartholomew
Name of person mailing paper

Date: March 7, 2002

Signature of person mailing paper